

AWARD NUMBER: W81XWH-15-1-0346

TITLE: Novel Diffusion-Weighted MRI for High-Grade Prostate Cancer Detection

PRINCIPAL INVESTIGATOR: Michael Abern, MD

CONTRACTING ORGANIZATION: University of Illinois

Chicago, IL 60612

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;

Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2017		2. REPORT TYPE Annual		3. DATES COVERED 15 Sep 2016 - 14 Sep 2017	
4. TITLE AND SUBTITLE Novel Diffusion-Weighted MRI for High-Grade Prostate Cancer Detection				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-1-0346	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Michael Abern MD; Brandon Caldwell BS; Virgilia Macias MD; Andre Kajdacsy-Balla PhD/MD; Richard Magin PhD; Joe Zhou PhD; Peter Gann ScD/MD E-Mail: mabern1@uic.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Illinois 820 S Wood St. CSN 515 M/C 955. Chicago, IL. 60612.				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Our initial findings illustrate the potential of the stretched exponential model parameters to better characterize high-grade prostate cancer. Additional work is underway to establish the correspondence between the DDC and a-maps with histological sections of the entire prostate gland. Given the technical difficulty with comparison of radical prostatectomy histology with imaging, we have also introduced a method to evaluate the accuracy of our novel diffusion imaging with biopsy histology.					
15. SUBJECT TERMS FROC, Prostate Cancer, MRI, Diffusion					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	25	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	8
5. Changes/Problems.....	8
6. Products.....	9
7. Participants & Other Collaborating Organizations.....	10
8. Special Reporting Requirements.....	10
9. Appendices.....	12

INTRODUCTION:

Accurate detection of aggressive prostate cancer (PCa) using existing clinical prediction tools is a challenge. Prostate MRI is promising technology for PCa detection and characterization. However, its accuracy has been sub-optimal especially in the setting of benign prostate inflammation or hyperplasia. We have developed a more sophisticated computational model of diffusion weighted MRI (FROC-DWI) that produces quantitative information regarding tissue architecture in-vivo. We hypothesize that the use of FROC-DWI in men with clinical suspicion for PCa will differentiate high grade PCa from indolent PCa and benign prostate pathology and therefore improve biopsy detection of aggressive PCa.

KEYWORDS:

FROC, Prostate Cancer, MRI, Diffusion

ACCOMPLISHMENTS:

What were the major goals of the project?

The major goal of the project is to generate a fractional order diffusion weighted (FROC) MRI signature that differentiates high grade prostate cancer (PCa) from low grade PCa and benign prostate tissues. The quantitative parameters of the FROC signature will be compared with histologic tissue architecture using RP specimens from our biorepository archive. The FROC diffusion parameters β , μ , and D will be correlated with stromal and epithelial architecture of areas of benign and malignant prostate tissue and a predictive model will be created to differentiate Gleason pattern 4 or higher PCa from other tissue types.

Aim 1: Generate a FROC MRI signature that differentiates high grade PCa from low grade PCa and benign prostate tissues

Aim 2: Validate the FROC MRI signature in a prospective patient cohort undergoing RP

What was accomplished under these goals?

Aim 1 accomplishments:

Year 1:

- IRB approval has been acquired for this aim
- The histology samples have been requested from the UIC biorepository for and digitized

- All MR images have been collected and prepared for image processing and analysis
- MR images have been de-identified and prepared in MatLab for quantitative analysis by the bioengineering co-investigators
- The histology specimens have all been retrieved and digitized so the grades of cancers can be outlined by the pathology co-investigators
- The UIC IRB has approved the continuing review of the protocol on 3/29/16
- 3 cases have had digital pathology annotation and MR image computation.
- Quality control testing of the MR imaging files has been completed.
- An abstract was presented to the IMPaCT conference for August 4-5 2016
- An abstract was presented to the ISMRM Workshop for September 11-16 2016

Year 2:

- The MatLab code for the production of alpha and DDC MRI maps was debugged, corrected, and finalized
- The MatLab code for co-registration of digital radical prostatectomy histology to T2 weighted MRI images of alpha and DDC maps to T2 weighted MRI was completed and tested
- 8 retrospective cases were analysed
- A new cohort of retrospective cases were added to the study to improve the sample size for model development : 30 patients that had pre-biopsy mpMRI and MRI targeted biopsies. This was approved in an IRB amendment.
- All MRI images for the added cohort have been collected and re-analysed
- Currently added cohort images are undergoing alpha and DDC map processing
- All biopsy pathologic data have been collected for the added cohort
- 2 abstracts were submitted to ISMRM 2018 conference – 1 for the initial results of the DDC/alpha map comparison to prostatectomy histology and 1 for the image co-registration methodology
- 1 abstract was submitted to the AUA 2018 conference with preliminary diagnostic accuracy thresholds for DDC and alpha parameters

Aim 2 accomplishments:

Year 1:

- The prospective experimental imaging protocol has been designed and approved by the collaborating radiology and bioengineering collaborators.
- The prospective prostatectomy sectioning protocol has been developed and approved by the IRB.

- The IRB protocol has been completed for Aims 2 and 3. Based on IRB and cancer center review, it was recommended to separate these into two separate protocols as the patients in aim 3 will be randomized. The IRB for aim 2 is completed and approved.
- The first subject enrollment under the prospective prostatectomy section (whole mount) has been scheduled for 10/14/16

Year 2:

- 5 subjects have been enrolled in the study
- Imaging and histologic digital processing is in progress
- The IRB continuing review was approved

What opportunities for training and professional development has the project provided?

Dr. Abern, the PI, proposed a training plan as part of this grant. He has initiated several of the objectives.

- He enrolled in the Masters of Science in Clinical and Translational Science program offered by the University of Illinois School of Public Health. He has completed HPA 472 (Clinical Research Methods 1), HPA 473 (Clinical Research Methods 2), HPA 479 (Evaluation of Clinical Interventions), with a grade of A. He completed BHIS 509 (Informatics for the Clinical Investigator) with a grade of B.
- He is currently enrolled in HPA 464 (Sociocultural Dimensions of Health Disparities) after which he will complete the UIC School of Public Health Clinical Research Methods certificate program.
- Dr. Gann has been teaching his course, Molecular Epidemiology and Biomarker Development (EPID512) , in a one-on-one fashion during weekly meetings
- He has attended the biweekly Works-in-Progress Seminar that includes participation from the Mentor's lab (Dr. Gann) as well as several other senior faculty members (including Dr. Gail Prins, Dr. Larissa Nonn) focusing on PCa.
- He attended the 2016 DOD IMPACT conference, which allowed for discussions and collaboration with several other DOD funded investigators.
- He attended the Prostate Cancer Foundation annual conference October 27-29, 2016.
- He was accepted for the EAU/AUA Exchange program for 2018 during which preliminary results from the studies supported by this grant will be presented.

How were the results disseminated to communities of interest?

For this reporting period two abstracts were submitted to the International Society of Magnetic Resonance Meeting in Paris, France and one to the American Urological Society 2018 conference in San Francisco, CA to be presented by the research team. These are pending acceptance and are attached to this report.

What do you plan to do during the next reporting period to accomplish the goals?

Aim 1:

- Complete the statistical analysis of the retrospective biopsy cohort
- Submit the analysis of the retrospective biopsy cohort to a scientific meeting for presentation
- Prepare the model development data (combined biopsy and prostatectomy data) for publication

Aim 2:

- Enroll 10 additional patients for the prospective cohort (validation)
- Complete the imaging processing for the model validation cohort
- Complete the statistical analysis of the model validation cohort
- Prepare the data for publication in a peer-reviewed journal

Aim 3:

- Determine the final imaging thresholds from Aims 1 and 2
- Design the prospective biopsy protocol using the thresholds
- Obtain IRB approval for Aim 3
- Begin patient enrollment for Aim 3

IMPACT:**What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

What was the impact on other disciplines?

The development of a whole mount prostatectomy grossing protocol will be beneficial for the Research Histology and Tissue Imaging Core at UIC.

The development of a methodology of digital prostate cancer annotation and mapping will provide a valuable resource for future projects.

The development of a new imaging co-registration method will be of interest to the scientific imaging community at large

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS:**Changes in approach and reasons for change**

The cost and effort required for quality analysis of radical prostatectomy histology has continued to be a challenge resulting in many unusable cases. We therefore added a new cohort to the model development : men who had MRI guided prostate biopsies. This will allow us to retrospectively perform post-processing on the MRI images to compute alpha and DDC maps and compare to the prostate biopsy pathology results, which is technically much easier and adds data to our model development.

Actual or anticipated problems or delays and actions or plans to resolve them

There is an anticipated change of staff. Brandon Caldwell, the primary research assistant, will likely transition to medical school at the end of the next reporting year. The plan is already in place to transition our current department clinical research coordinator, Ruben Sauer, to the project for the final year. This phase of the project will primarily entail patient enrollment and regulatory tasks on the biopsy aim of this project which is Ruben

Sauer's current role on other prostate cancer clinical trials so I anticipate a smooth transition.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

1. Michael Abern MD, Brandon Caldwell BS, Virgilia Macias MD, Winnie Mar MD, Karen Xie MD, Andre Kajdacsy-Balla PhD/MD, Richard Magin PhD, Joe Zhou PhD, Peter Gann ScD/MD; *High Grade Prostate Cancer Characterization Using Fractional Order Calculus Diffusion Weighted MRI*; 2016; Abstract and poster for PCRP IMPaCT Conference; Presented 10/2016; Yes (federally supported)
2. Meltem Uyanik MS, Michael Abern MD, Brandon Caldwell BS, Muge Karaman PhD, Winnie Mar MD, Joe Zhou PhD, Richard L. Magin PhD; *Prostate Cancer Classification Using a Stretched Exponential Model of*

Diffusion; 2016; Abstract and poster for ISMRM Workshop; Presented 9/2016; No

3. Brandon Caldwell BS , Meltem Uyanik MS, Michael Abern MD, Virgilia Macias MD, Cristian Luciano PhD, Richard L. Magin PhD; *A methodology for Registering Prostate Histology and Radiologic Imaging to Validate Prostate Cancer Detection in 2D*; 2017; Abstract for ISMRM Congress; Submitted; No
4. Brandon Caldwell BS , Meltem Uyanik MS, Virgilia Macias MD, Winnie Mar MD, Richard L. Magin PhD, Michael Abern MD; *Fractional order calculus model of magnetic resonance diffusion weighted imaging for high grade prostate cancer detection*; 2017; Abstract for AUA Congress; Submitted; No
5. Meltem Uyanik MS, Michael Abern MD, Brandon Caldwell BS, Muge Karaman PhD, Winnie Mar MD, Virgilia Macias MD, Xiaohong Joe Zhou PhD, Richard L. Magin PhD; *Prostate Cancer Classification Using Stretched Exponential Model Parameters of Diffusion Signal Decay*; 2017; Abstract for ISMRM Congress; Submitted; No

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Michael Abern, MD

Project Role: PI

Researcher Identifier: mabern

Nearest person month worked: $12 \times 0.4 = 4.8$

Contribution to Project: Dr. Abern has acted as the project lead

Name: Peter Gann, MD

Project Role: Co-mentor

Researcher Identifier: pgann

Nearest person month worked: $12 \times 0.1 = 1.2$

Contribution to Project: Dr. Gann has contributed as mentor for the histologic analytic aspects of the project, and has conducted bi-weekly meetings with the PI

Name: Andre Balla, MD/PhD

Project Role: Pathology consultant

Researcher Identifier: aballa

Nearest person month worked: $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Balla has consulted regarding the tissue preparation of the prostatectomy specimens for Aim 2

Name: Virgilia Macias, MD

Project Role: Pathology consultant

Researcher Identifier: vmacias

Nearest person month worked: $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Macias has assisted in screening the retrospective pathology samples for adequacy for analysis

Name: Xiaohong “Joe” Zhou, PhD

Project Role: Co-mentor

Researcher Identifier: xjzhou

Nearest person month worked: $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Zhou has contributed by holding bi-weekly meetings with the PI and consulting regarding the MR processing for aim 1, and for the scan protocol for aim 2

Name: Brandon Caldwell

Project Role: Study Coordinator

Nearest person month worked: $12 \times 0.50 = 6$

Contribution to Project: Mr. Caldwell has contributed to the study via IRB management and submissions, Cancer Center compliance and research design.

Name: Richard Magin, PhD

Project Role: Mathematical image analysis team

Researcher Identifier: rmagin

Nearest person month worked: $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Magin has contributed as the designer of the FROC model and supervisor of the MR image processing

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Nothing to report.

QUAD CHARTS:

Nothing to report.

APPENDICES:

Please see the attached submitted meeting abstracts.

Fractional order calculus model of magnetic resonance diffusion weighted imaging for high grade prostate cancer detection

Brandon Caldwell BS^{1,2}, Meltem Uyanik PhD², Virgilia Macias MD³, Winnie Mar MD⁴, Richard Magin PhD², Michael Abern MD¹

¹Department of Urology, University of Illinois at Chicago College of Medicine, Chicago, IL, United States

²Department of Bioengineering, University of Illinois at Chicago College of Engineering, Chicago, IL, United States

³Department of Pathology, University of Illinois at Chicago College of Medicine, Chicago, IL, United States

⁴Department of Radiology, University of Illinois at Chicago College of Medicine, Chicago, IL, United States

Introduction and objective: Multi-parametric magnetic resonance imaging (mpMRI) is used to inform treatment decisions for prostate cancer but suffers from poor specificity when differentiating benign from malignant prostate lesions and lacks quantitative parameters outside the apparent diffusion coefficient (ADC). We propose the use of α ($0 < \alpha < 1$), a tissue heterogeneity index studied in brain, for prostate. In this study, we attempt to perform pixel-by-pixel validation.

Methods: A patient with a pre-radical prostatectomy 3T mpMRI (GE Healthcare, Discovery 750 MRI), using b-values of 50 to 2000, was identified. Histology was stained with Hematoxylin and Eosin before digitization (ScanScope CS, Aperio) and annotation by Gleason score (GS) (3-5); pseudo-whole mount levels from the specimen were reconstructed. Known z-axis resolution allows for the matching of histology image (HI) and radiologic image (RI) levels. Registration of HI to RI utilized a linear piecewise affine non-rigid transformation. α , DDC, and D (ADC) values were calculated pixel-by-pixel from diffusion weighted imaging (DWI) values using single ($S = S_0 \exp[-b \cdot \text{ADC}]$) and stretched ($S = S_0 \exp[-(b \cdot \text{DDC})^\alpha]$) exponential models. b-50 and b-500 were used to calculate D. Accuracy of registration was tested by contour matching and percent area overlap. ROC curves were generated for the case (9 histological levels) with comparisons to $\text{GS} \geq 3$ (all tumors) and $\text{GS} \geq 4$ (clinically significant tumors).

Results: Figure 1 shows ROC results. For $\text{GS} \geq 3$: α , AUC = 0.566; DDC, AUC = 0.682; D, AUC = 0.691. For $\text{GS} \geq 4$: α , AUC = 0.600; DDC, AUC = 0.640; D, AUC = 0.625. On average, 92.9% of HI was registered within its matching RI contour.

Conclusions: Except α vs. $\text{GS} \geq 3$, all AUC values were more than 0.60, demonstrating a level of success in validating RI modalities. With the exception of α , all GS comparisons had a higher AUC for $\text{GS} \geq 3$ than $\text{GS} \geq 4$; α may contribute to more clinically significant results. Accurate registration will allow for the determination of an imaging modality or a combination of modalities that can best stage and detect PCa. Future work includes automation, a larger cohort, and 3D registration.

Source of Funding: This research was supported by Department of Defense PRTA W81XWH-15-1-0346 (Abern).

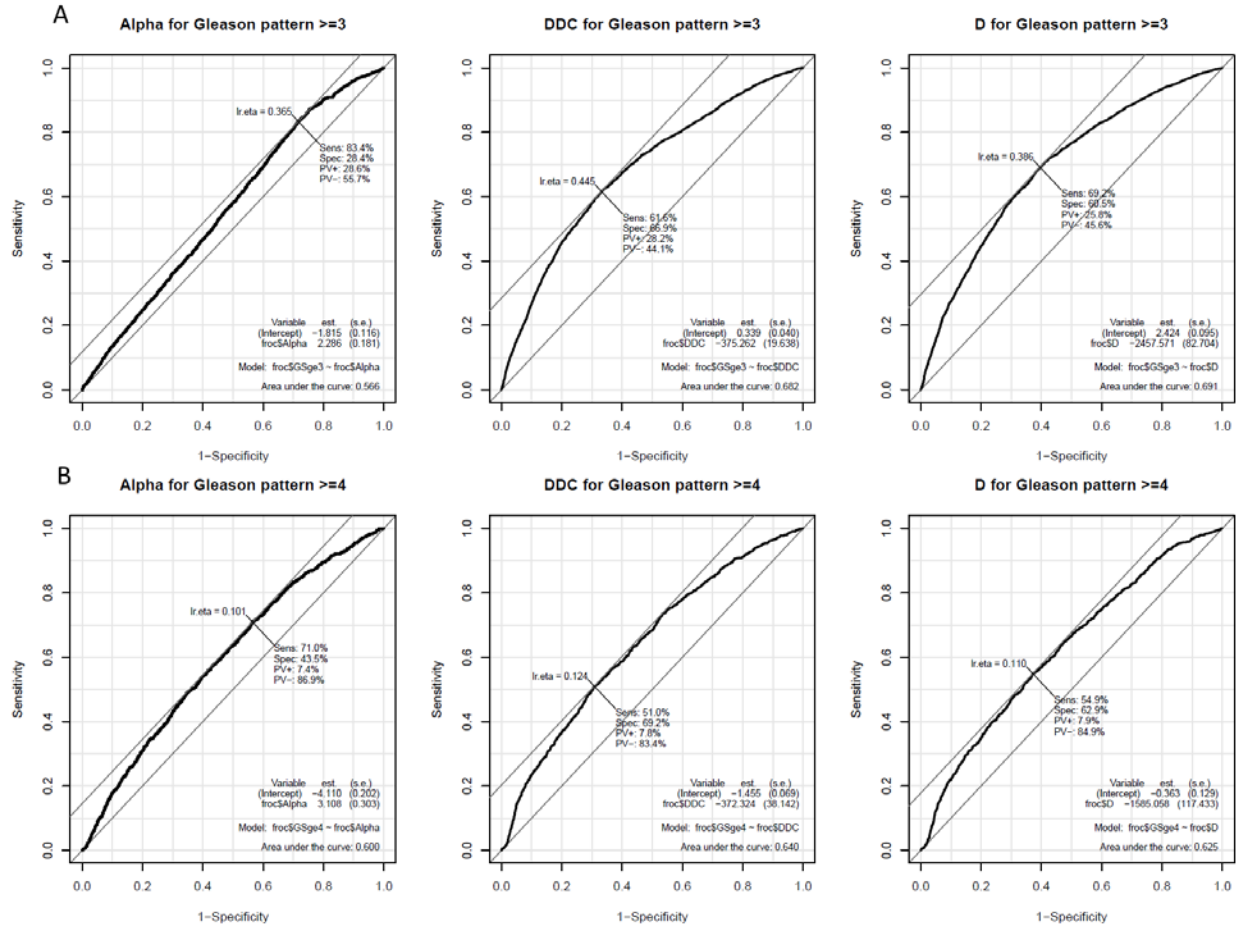


Figure 1: ROC curves for **A)** $GS \geq 3$ and **B)** $GS \geq 4$. **A)** α vs. $GS \geq 3$: AUC = 0.566; Sensitivity = 83.4%; Specificity = 28.4%. DDC vs $GS \geq 3$: AUC = 0.682; Sensitivity = 61.6%; Specificity = 66.9%. D vs $GS \geq 3$: AUC = 0.691; Sensitivity = 69.2%; Specificity = 60.5% **B)** α vs. $GS \geq 4$: AUC = 0.600; Sensitivity = 71.0%; Specificity = 43.5%. DDC vs $GS \geq 4$: AUC = 0.640; Sensitivity = 51.0%; Specificity = 69.2%. D vs $GS \geq 4$: AUC = 0.625; Sensitivity = 54.9%; Specificity = 62.9%.

A Methodology Towards Registering Prostate Histology and Radiologic Imaging to Validate Prostate Cancer Detection in 2D

Brandon Caldwell BS^{1,2}, Meltem Uyanik PhD², Michael Abern MD¹, Virgilia Macias MD³, Cristian Luciano PhD², Richard Magin PhD²

¹Department of Urology, University of Illinois at Chicago College of Medicine, Chicago, IL, United States

²Department of Bioengineering, University of Illinois at Chicago College of Engineering, Chicago, IL, United States

³Department of Pathology, University of Illinois at Chicago College of Medicine, Chicago, IL, United States

Synopsis: In-vivo radiological imaging is used globally to detect possible cancers and inform treatment decisions, but difficulties arise when attempting to compare radiological findings to the gold-standard of diagnosis, histopathology. Standard imaging protocols have documented success but to determine the reliability of new imaging sequences and modalities, correlation to histopathology must be made. Several methods have been proposed for registration in both 2D and 3D, but these have shown limited effectiveness and often require unique equipment or proprietary algorithms. In this study, we attempt to complete an accurate registration in 2D in order to validate different imaging modalities.

Introduction: Multi-parametric magnetic resonance imaging (mpMRI) is currently in standard use for men with suspicion of prostate cancer (PCa) to inform treatment decisions¹. Matching in-vivo mpMRI to embedded radical prostatectomy (RP) sections, however, is a challenging process due to the vast differences in resolution and scale. In order to evaluate new imaging modalities, the correlation between imaging and histology is critical. Previous studies^{2,3,4} have proposed matching internal landmarks, the use of cutting devices, fiducials, landmark creation, and matching contours; these methods are generally not reliable, require atypical equipment, or can potentially harm the diagnostic integrity of the specimen. In this study we demonstrate the ability to register histological images (HI) to their corresponding radiologic image (RI) and use Gleason score (GS) annotations to perform pixel-by-pixel validation.

Methods: Cohort: A patient with a pre-RP 3T mpMRI (GE Healthcare, Discovery 750 MRI) was identified. Pathological Processing: The prostate was fixed before sectioning to ensure even slices and enable thinner levels (3mm). Quartered levels were embedded in paraffin and stained with Hematoxylin and Eosin (H&E) before placement in glass slides which were scanned at 20X (Scanscope CS, Aperio Technologies) and digitally annotated (Aperio ImageScope, Leica Biosystems) by a board-certified pathologist. The quarters were annotated in pure RGB colors by GS (3, 4 and 5) and for orientation (clock face positions). Pure colors are chosen to be reliably detected in MATLAB v2017b (MathWorks, Natick, MA). A pseudo-whole mount (PWM) slice can be reconstructed from the collective quarters. Histological/Radiological Slice Matching: Slice location is determined with consideration to slice thickness and relative location from the apex. 3mm MRI slices create a reference by which histological levels can be iteratively compared to, shown in Figure 1, consistent with previous work⁵. Diffusion Value Calculations: Diffusion-weighted MRI (DWI) uses a single exponential signal decay model, $S = S_0 \exp[-b \cdot \text{ADC}]$, to generate a spatial map of the apparent diffusion coefficient (ADC). To quantify tissue heterogeneity in the brain, Bennett et al.⁶ proposed a stretched-exponential model, $S = S_0 \exp[-(b \cdot \text{DDC})^\alpha]$, where DDC is the distributed diffusion coefficient, and α ($0 < \alpha < 1$) is a heterogeneity index, characterizing the multi-exponential nature of diffusion-related signal decay⁷; here we apply it to prostate. α , DDC, and D were calculated on a pixel-by-pixel basis by fitting the DWI signal intensities (SIs) to the stretched- or mono-exponential model, respectively. T2 (T2 weighted image) SI values were generated with the “dicomread” function in MATLAB. Registration Function: “process_H” was created in MATLAB for registration. The scale (mm) of the PWM was determined using ImageScope and applying a fixation correction factor (1.047)^{8,9}. Manual control point registration (“cpselect”, MATLAB) applies a linear piecewise affine non-rigid transformation. “process_H” outputs the transformed HI (Figure 2A) and qualitative assessments (Figure 2C & D). Registration Accuracy: Accuracy of registration was tested by contour matching, shown in Figure 3, and percent area overlap of HI to RI. MRI Validation: ROC curves were generated for a single slice. Masks were created demarking $\text{GS} \geq 3$ (all tumors) and $\text{GS} \geq 4$ (clinically significant tumors)¹⁰ from the processed HI, providing Boolean diagnosis designations for ROC comparison, pixel by pixel.

Results: Figures 4 and 5 show ROC results generated (“Epi,” “pROC,” R3.4.0, RFSCP) for each imaging modality as compared to $\text{GS} \geq 3$ (Figure 4) and $\text{GS} \geq 4$ (Figure 5). When compared to $\text{GS} \geq 3$, DDC provided the highest AUC (0.802) and specificity (76.2%); α provided the highest sensitivity (96.4%). When compared to $\text{GS} \geq 4$, DDC provided the highest AUC (0.769), T2

provided the highest specificity (68.9%), and D provided the highest sensitivity (87.5%). Only α and T2 increased AUC when compared to $GS \geq 4$ (0.614 to 0.702 and 0.552 to 0.676, respectively). Area-based comparison showed 75.8 % and 90.38% area overlap for the DWI-based and T2-based registrations, respectively.

Discussion and Conclusion: Except for T2 vs $GS \geq 3$, all comparison AUC values were more than 0.60, demonstrating a level of success in validating RI modalities. Increases in AUC from $GS \geq 3$ to $GS \geq 4$ are promising for those modalities (α and T2) to preferentially detect higher grade tumors and avoid overtreatment. Limitations in this study include distortion from catheter placement, conceded because the peripheral zone is the most likely to develop PCa¹¹, and HI slices are cut $\sim 5\mu\text{m}$ thick so it is not reasonable to assume a true 1:1 slice match. Accurate registration will allow for the determination of an imaging modality or a combination of modalities that will best stage and detect PCa. Future work includes automation, a larger cohort, and 3D registration.

Acknowledgements:

This research was supported by Department of Defense PRTA W81XWH-15-1-0346 (Abern).

References:

- [1] Barentsz JO, Richenberg J, Futterer JJ, et al. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012;22(4):746-57
- [2] Park H, Piert M, Meyer C. Registration methodology for histological sections and in vivo imaging of human prostate. *Acad Radiol* 2008; 15:1027-1039
- [3] Yamamoto H, BChir MB, Chandra A, et al. A workflow to improve the alignment of prostate imaging with whole-mount histopathology. *Acad Radiol.* 2014;21:1009-1019
- [4] Commandeur F, Acosta O, Crevoisier R, et al. Prostate whole-mount histology reconstruction and registration to MRI for correlating in-vivo observations with biological findings. *IEEE Eng. Med. Biol. Soc.* 2015;2015:2399-2402
- [5] Guzman L, Commandeur F, Crevoisier R, et al. Slice correspondence estimation using SURF descriptors and context-based search for prostate whole-mount histology MRI registration. *IEEE Eng Med Biol Soc.* 2016 Aug;2016:1163-1166
- [6] Bennett, K. M., et al. Models of diffusion signal decay in magnetic resonance imaging: capturing complexity. *Magn. Reson. Med.* 50 (2003): 727-734
- [7] Berbian- Santos, M.N. et al. Mathematical functions for the analysis of luminescence decays with underlying distributions 1. Kohlrausch decay function (stretched exponential). *Chem. Phys.* 315 (2005): 171-182
- [8] Jonmarker S, Valdman A, Egevad L, et al. Tissue shrinkage after fixation with formalin injection of prostatectomy specimens. *Virchows Arch.* 2006 Sep; 449(3): 297–301
- [9] Schned AR, Karlya WJ, Harris RJ, et al. Tissue shrinkage correction factor in the calculation of prostate cancer volume. *The American Journal of Surgical Pathology.* 1996 Dec;20(12):1501-1506
- [10] Miah S, Ahmed H, Emberton M. Does true Gleason pattern 3 merit its cancer descriptor? *Nature Reviews Urology.* 2016 Aug;13:541-548
- [11] McNeal JE, Redwine EA, Freiha FS, Stamey TA. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. *Am J Surg Pathol.* 1988;12:897-906

Figures

		T2 Image #	DWI Image #	ADC Image #	Histology
Apex	1	3538	3342	3477	Apex 1 2 3 4 5 6 7 8 9 10 11 Base
	2	3539	3343	3478	
	3	3540	3344	3479	
	4	3541	3345	3480	
	5	3542	3346	3481	
	6	3543	3347	3482	
	7	3544	3348	3483	
	8	3545	3349	3484	
	9	3546	3350	3485	
	10	3547	3351	3486	
	11	3548	3352	3487	
	12	3549	3353	3488	
	13	3550	3354	3489	
Base/SV	14	3551	3355	3490	

Figure 1: Slice matching from T2 reference. T2, DWI (diffusion weighted images), and ADC have similar Z-axis resolution (3mm) and so can be compared iteratively from the point at which the prostate apex first appears. Histological slices can be matched by considering the thickness of apex and base cuts (~5mm), and the thickness of each level's slice (3mm).

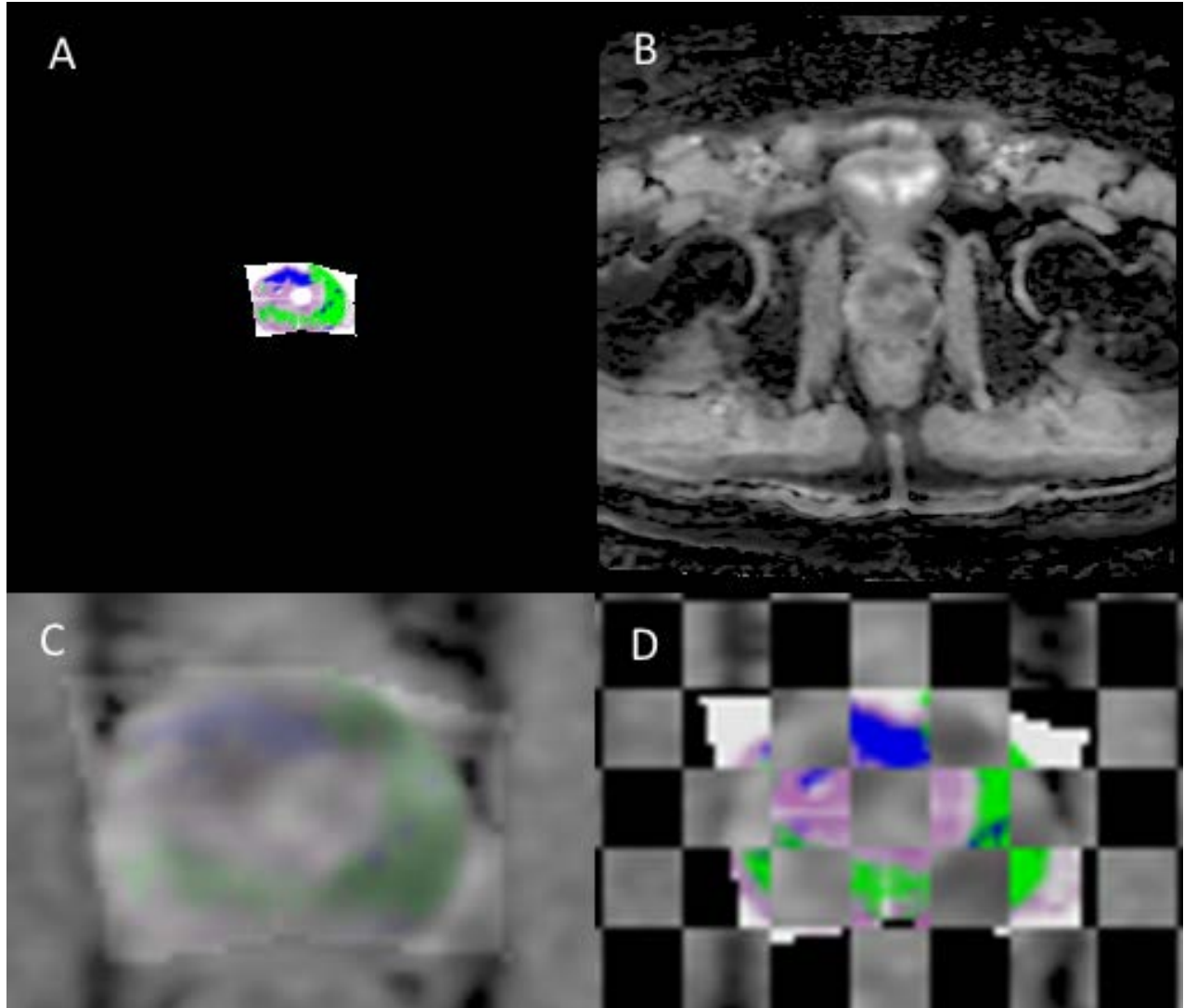


Figure 2: Registration outputs from “process_H.” Qualitative comparisons. **A)** Transformed and control point registered HI. Annotations were filled in by “process_H.” GS 3 is green, GS 4 is blue, and GS 5 would be red if present. **B)** Fixed reference ADC image used for registration. **C)** Zoomed in processed HI overlaid with transparency onto ADC image. **D)** Zoomed in processed HI checkerboard overlayed onto ADC image.

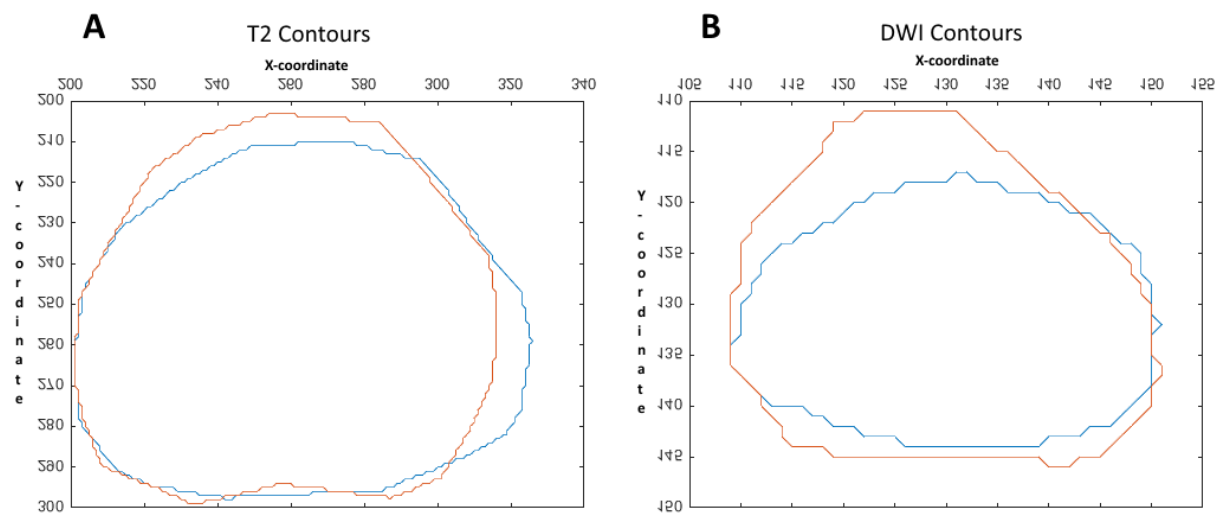


Figure 3: Contour matching. A) Contours for histology (blue) and T2 (512x512 base matrix) prostate (orange) overlaid. 90.38% of RI captured by HI. **B)** Contours for histology (blue) and DWI-based (256x256 base matrix) imaging modalities (orange). 75.8% of RI captured by HI.

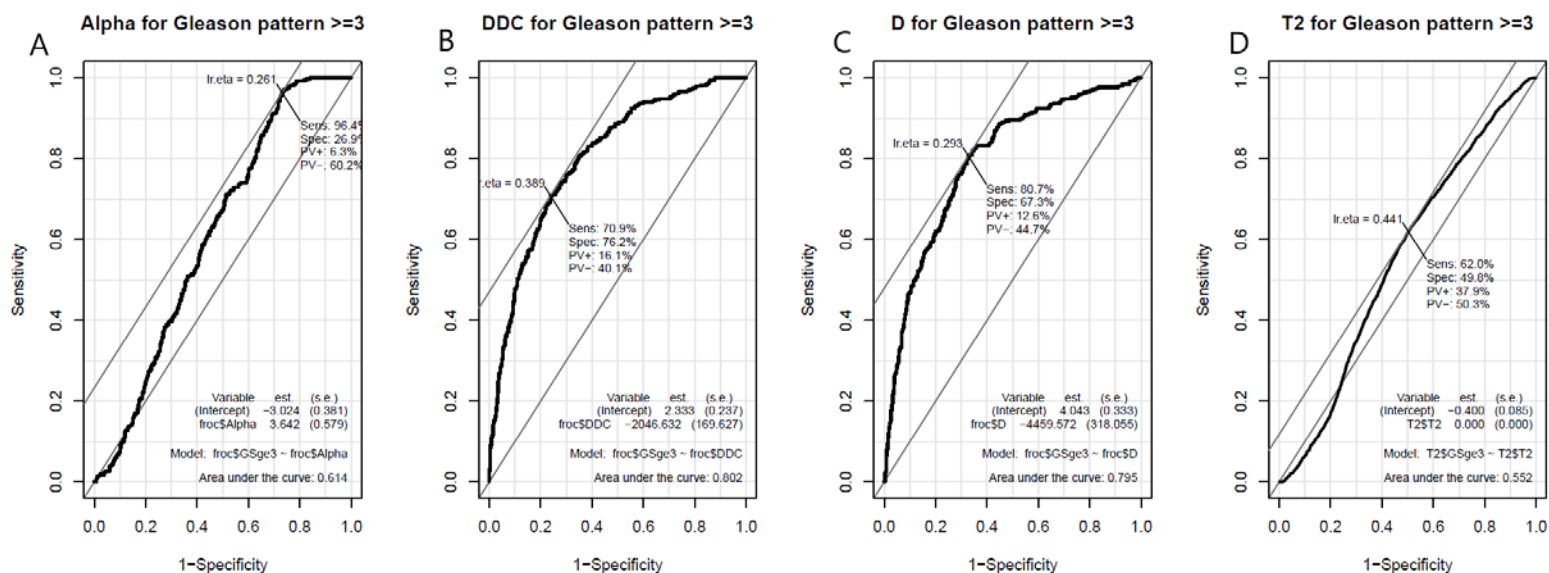


Figure 4: ROC curves for GS ≥ 3 calculated with R packages. **A)** α vs. GS ≥ 3 : AUC = 0.614; Sensitivity = 96.4%; Specificity = 26.9% **B)** DDC vs GS ≥ 3 : AUC = 0.802; Sensitivity = 70.9%; Specificity = 76.2% **C)** D vs GS ≥ 3 : AUC = 0.795; Sensitivity = 80.7%; Specificity = 67.3% **D)** T2 vs GS ≥ 3 : AUC = 0.552; Sensitivity = 62.0%; Specificity = 49.8%

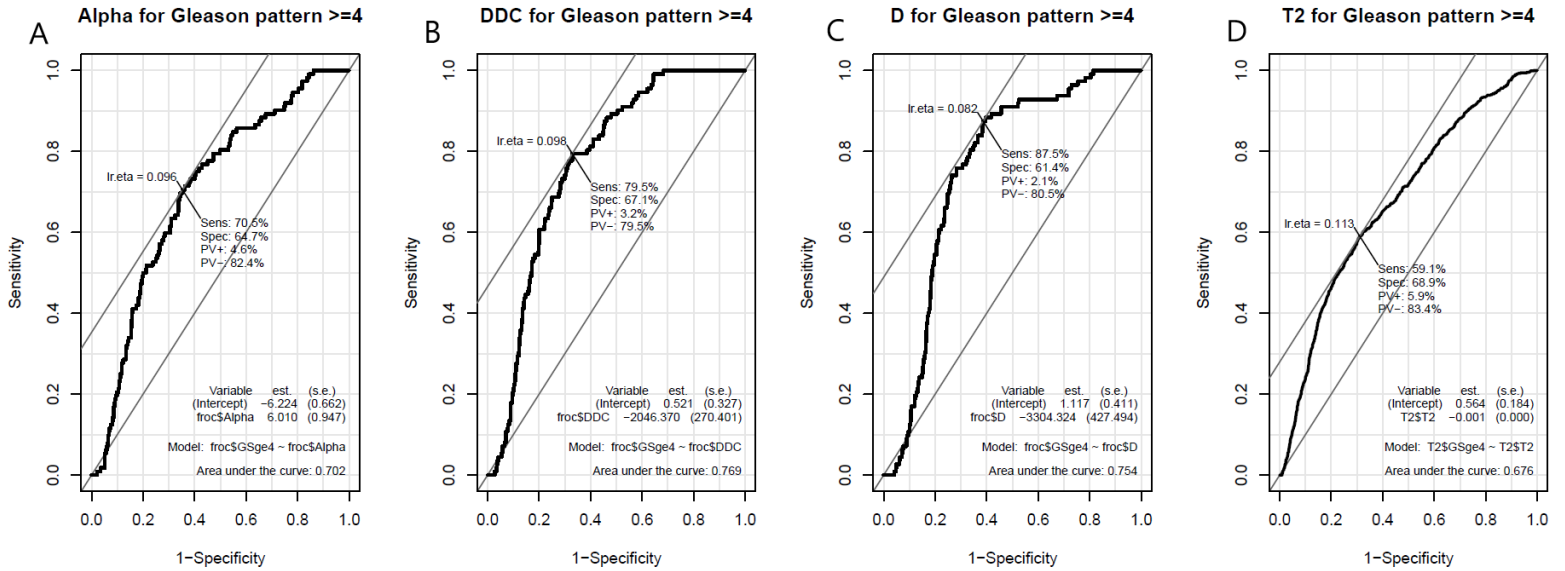


Figure 5: ROC curves for $\text{GS} \geq 4$ calculated with R packages. **A)** α vs. $\text{GS} \geq 4$: AUC = 0.702; Sensitivity = 70.5%; Specificity = 64.7% **B)** DDC vs $\text{GS} \geq 4$: AUC = 0.769; Sensitivity = 79.5%; Specificity = 67.1% **C)** D vs $\text{GS} \geq 4$: AUC = 0.754; Sensitivity = 87.5%; Specificity = 61.4% **D)** T2 vs $\text{GS} \geq 4$: AUC = 0.676; Sensitivity = 59.1%; Specificity = 68.9%

Prostate Cancer Classification Using Stretched Exponential Model Parameters of Diffusion Signal Decay

Meltem Uyanik¹, Michael Abern², Brandon Caldwell², Muge Karaman³, Winnie Mar⁴, Virgilia Macias⁵, Xiaohong Joe Zhou^{1,3,4,6}, and Richard Magin⁷

¹Richard and Loan Hill Department of Bioengineering, University of Illinois at Chicago, Chicago, IL, United States, ²Urology, University of Illinois at Chicago, Chicago, IL, United States, ³Center for Magnetic Resonance Research, College of Medicine, University of Illinois at Chicago, Chicago, IL, United States, ⁴Radiology, University of Illinois at Chicago, Chicago, IL, United States, ⁵Pathology, University of Illinois at Chicago, Cahicago, IL, United States, ⁶Neurosurgery, University of Illinois at Chicago, Chicago, IL, United States, ⁷Richard and Loan Hill Department of Bioengineering, University of Illinois, Chicago, IL, United States

Synopsis

Prostate cancer is a common malignancy among men. Using MRI to discriminating high-grade disease from benign and indolent cancer in the prostate is highly desirable for treatment planning. Single and multi- exponential models of diffusion signal decay in the prostate has proven useful for determining prostate cancer tissue structure. However, classification of cancer grade remains illusive. In this study, we investigate the stretched exponential signal decay model using histology and ROC analysis to determine if it will more accurately characterize aggressive prostate cancer.

Introduction

Prostate cancer is one of the most common malignancy among men in the US [9]. Diffusion-weighted MRI (DWI) plays an important role in providing important biological information on regional changes in prostate tissue. The most commonly used method for DWI is a single exponential signal decay to generate a spatial map of the apparent diffusion coefficient (ADC, mm2/s). DWI studies of the prostate showed the usefulness of single exponential signal decay on noninvasively determining human tissue structure [4],[8],[10]. However, diffusion weighted signal decay in the prostate does not follow a single exponential pattern and therefore, it is inadequate to differentiate between benign prostate inflammation and hyperplasia [3]. To overcome this problem, Bennett et al. [1] introduced the stretched exponential model. It has been shown that the stretched exponential signal decay model parameters provide more information about tumor than ADC [5-7]. In this study, we show the ability of using a stretched exponential model to establish the correspondence between the DDC and α -maps with histological sections of the entire prostate gland to characterize aggressiveness of prostate cancer.

Methods

Patients. This study enrolled a total of 10 patients with high-grade proven prostate cancer. **Imaging.** (a) MR Protocol. Patients were scanned on a 3T multi-parametric MRI (GE Healthcare, Discovery 750 MRI), Figure 1a, prior to radical prostatectomy (RP). DWI images (TR 2500 ms, TE 68 ms, FOV 28x28 cm2, matrix 256x256, resolution 1.09 mm) were acquired at multiple b-values (50, 500, 1000, 1500, and 2000 s/mm2) with the corresponding averages (2, 4, 8, 12, and 16). The slice thickness was 3 mm for all sequences. (b) Histology Protocol. Whole embedded RP sections were digitized at 20X magnification using a digital scanner (Scanscope CS, Aperio Technologies), and all tumor foci were annotated (Aperio ImageScope 11.2.0.780, Leica Biosystems) by Gleason pattern (Figure 1b) by a board certified genitourinary pathologist. A zonal scheme was devised for matching the MRI to the RP sections based on the orientation to the urethra (anterior/posterior, left/right, level from base to apex). **Model fitting.** The multi-b-value diffusion data were fitted to the mono-exponential model. using the following equation:

$$S = S_0 e^{(-b \times ADC)}$$

To quantify the degree of tissue heterogeneity, the multi-b-value diffusion data were fitted to the stretched exponential model, [1] using the following equation:

$$S = S_0 e^{[-(b \times DDC)^\alpha]}$$

where DDC (mm2/s) is the distributed diffusion coefficient , and α (0 < α < 1) is a heterogeneity index that characterizes the multi-exponential nature of diffusion-related signal decay [2]. The data was fit pixel by pixel for selected slices to the mono-exponential and to the stretched-exponential models using a nonlinear least squares fitting algorithm in Matlab (MathWorks). **Statistical Analysis.** Fifty-two (52) target quadrant regions were identified as healthy or unhealthy from one patient. The performance of the stretched exponential model for differentiating between benign prostate inflammation and hyperplasia was evaluated and compared with the mono-exponential model using a receiver operating characteristic (ROC) analysis. ROIs were drawn by using the means of each quadrants of ADC, DDC, and α. Multivariate logistic regression was used to combine the stretched exponential model parameters (DDC, and α). All statistical analyses were carried out using Matlab (MathWorks).

Results

Figure 2 shows a whole prostate ADC, DDC, and α maps from a representative patient. Figure 3a shows the group analysis as presented in the boxplots of the mean ADC, DDC, and α. Figure 3b shows the corresponding descriptive statistics, exhibiting sample mean and standard deviation, (±σ), of ADC, DDC, and α for healthy and unhealthy. All parameters show significant differences (p-values<0.05) between healthy and unhealthy. Figure 4 shows the ROC results for the ADC, DDC, α, and combined (DDC,α) parameters. The ROC of combined (DDC,α) parameters yielded the highest sensitivity (0.857), and area under the curve (AUC = 0.874).

Discussion and Conclusion

ADC maps are sensitive to regional changes in prostate tissue, however, their diagnostic specificity is not enough for distinguishing between benign prostate inflammation and hyperplasia [3]. The results showed that the stretched-exponential model with multi-b values diffusion data has potential in establishing the correspondence between the DDC and α -maps with histological sections of the entire prostate gland. The ROC analysis showed that the combination of the stretched exponential model parameters is more accurate of differentiating high grade prostate cancer from benign and indolent prostate cancer.

Acknowledgements

This research was supported by Department of Defense PRTA W81XWH-15-1-0346 (Abern).

References

[1] Kevin M Bennett et al. Characterization of continuously distributed cortical water diffusion rates with a stretched-exponential model. Magnetic resonance in medicine, 50(4):727–734, 2003.

[2] MN Berberan-Santos et al. Mathematical functions for the analysis of luminescence decays with underlying distributions 1. kohlrusch decay function (stretched exponential). Chemical Physics, 315(1):171–182, 2005.

[3] Jonathan I Epstein et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified gleason grading system and factoring in tertiary grades. European urology, 61(5):1019–1024, 2012.

[4] Kazuhiro Kitajima, Yasushi Kaj et al. Prostate cancer detection with 3 t mri: Comparison of diffusion-weighted imaging and dynamic contrast-enhanced mri in combination with t2-weighted imaging. Journal of Magnetic Resonance Imaging, 31(3):625–631, 2010.

[5] Thomas C Kwee et al. Intravoxel water diffusion heterogeneity imaging of human high-grade gliomas. NMR in biomedicine, 23(2):179–187, 2010.

[6] Xiaohang Liu et al. Comparison of stretched-exponential and mono-exponential model diffusion-weighted imaging in prostate cancer and normal tissues. Journal of Magnetic Resonance Imaging, 42(4):1078–1085, 2015.

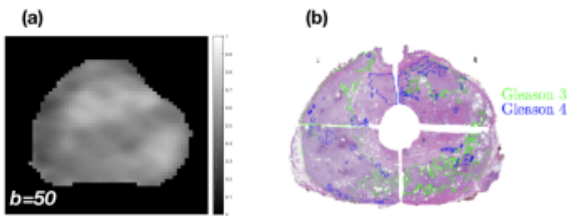
[7] Yousef Mazaheri et al. Diffusion-weighted magnetic resonance imaging of the prostate: improved robustness with stretched exponential modeling. Journal of computer assisted tomography, 36(6):695–703, 2012.

[8] Rajakumar Nagarajan et al. Correlation of gleason scores with diffusion-weighted imaging findings of prostate cancer. Advances in urology, 2012, 2011.

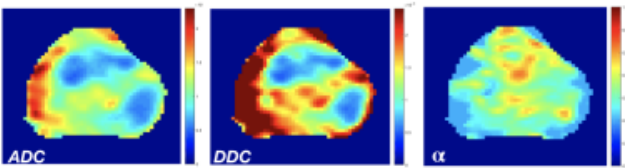
[9] Lindsey A Torre et al. Jemal. Global cancer statistics, 2012. CA: a cancer journal for clinicians, 65(2):87–108, 2015.

[10] Bashar Zelhof et al. Correlation of diffusion-weighted magnetic resonance data with cellularity in prostate cancer. BJU international, 103(7):883–888, 2009.

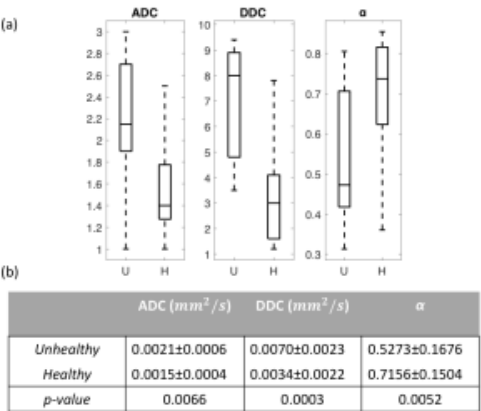
Figures



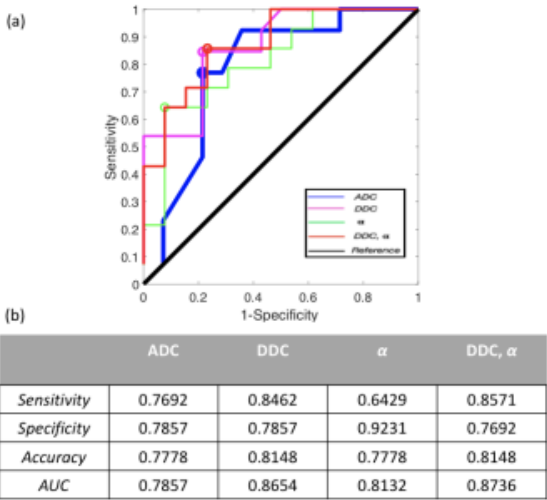
(a) The prostate gland is in an axial DW normalized MR image ($b= 50$ s/mm²) at the mid-base region of the prostate. (b) Annotated prostate at approximate level of MRI. Prospectively, this will be done in true whole mount and with a pure two-color scheme.



Maps of ADC, DDC, and α maps from a representative patient. ADC map (mm²/s ¹⁰⁻³) is fitted to the mono-exponential model. DDC (mm²/s¹⁰⁻³) and α maps are fitted to the stretched-exponential model. FOV: 7 ×7 cm².



(a) Boxplots of the mean values of the stretched exponential model parameters (ADC, DDC, and α). (b) The corresponding descriptive statistics, showing sample mean and standard deviation, ($\pm\sigma$), of ADC, DDC, and α for healthy, and unhealthy groups. All parameters are exhibiting significant differences (p-values<0.05).



(a) The ROC curve of using the ADC, DDC, α , and combined (DDC, α) for characterizing aggressive prostate cancer. (b) Summary of the corresponding best cut-off sensitivity and specificity values (shown as circles in the curves) as well as the accuracy and the AUC for the ROC curves. The combination of stretched exponential model the parameters were obtained by using a multivariate logistic regression algorithm.